A Simple and Environmentally Benign Protocol for Biginelli Reactions Catalyzed by Silica-Bonded *S*-Sulfonic Acid

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Abstract: A protocol for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones was developed by means of a three-component condensation of an aldehyde, a β -dicarbonyl compound, and urea or thiourea in acetic acid catalyzed by silica-bonded *S*-sulfonic acid. Compared to the classical Biginelli reaction conditions, this new protocol has the advantages of consistently excellent yields and short reaction times. After the reaction, the catalyst could be recovered easily and reused with little change in its activity.

Key words: Biginelli reaction; silica-bonded *S*-sulfonic acid; dihydropyrimidinone

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Organic syntheses in which heterogeneous acid catalysts [1] are used in place of homogeneous acid reagents have received much attention owing to their potential for use in the development of green [2] and sustainable chemical processes [3]. Reactions catalyzed by solid acids have the potential to be safe and highly atom efficient, and they typically involve simple workup procedures that do not produce large amounts of salt wastes [4]. In recent decades, dihydropyrimidinones and their derivatives have drawn attention because of their antibacterial, antiviral, antitumor, and anti-inflammatory activities [5]. For example, Biginelli compounds (3,4-dihydropyrimidin-2(1*H*)-ones) act as calcium channel blockers, antihypertensive agents, a 1A-antagonists, and neuropeptide Y antagonists [6–9]. Batzelladine B, an alkaloid isolated from a marine sponge, contains a dihydropyrimidine unit and shows anti-HIV activity [10]. Numerous procedures for preparing dihydropyrimidinones have been reported, involving reagents and catalysts such as $\text{H}_4\text{PMo}_{11}\text{VO}_{40}$ [11], Dowex-50W [12], $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$ [13], MgBr_2 [14], polymer-supported 4-aminoformoyldiphenylammonium triflate [15], $\text{NaHSO}_4/\text{SiO}_2$ [16], FeCl_3 [17], ZrCl_4 [18], $\text{Cu}(\text{OTf})_2$ [19],

$\text{Bi}(\text{OTf})_3$ [20], ytterbium triflate [21], $\text{NH}_2\text{SO}_3\text{H}$ [22], 12-molybdophosphoric acid [23], natural HEU-type zeolites [24], $\text{Sr}(\text{OTf})_2$ [25], $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ [26], silica triflate [27], $\text{Fe}(\text{HSO}_4)_3$ [28], TCICA [29], PPh_3 [30], melamine trisulfonic acid [31], Fe_3O_4 nanoparticles [32], sulfonated β -cyclodextrine [33], metal hydrogen sulfates [34], ionic liquids [35–37], and sulfonated carbon materials [38].

However, some of these procedures require expensive reagents, strongly acidic conditions, long reaction times, high temperatures, or stoichiometric amounts of catalysts, or they result in environmental pollution or give unsatisfactory yields. Therefore, there is a need for new catalysts that are readily available or easy to prepare, inexpensive, and recoverable (hence reusable and environmentally friendly). Moreover, the workup procedure should be simple. In this regard, functionalized silica particles and mesoporous silica materials have been synthesized and have found many applications [39–43]. As part of our continuing studies of organic processes mediated by heterogeneous acid catalysts, we now report a highly efficient synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones (Scheme 1) by means of a three-component condensation reaction catalyzed by sil-

Scheme 1. SBSSA-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones.

ica-bonded *S*-sulfonic acid (SBSSA).

1 Experimental

SBSSA was prepared according to Refs. [44,45]. In a general procedure, a mixture of an aldehyde (2 mmol), a β -dicarbonyl compound (2 mmol), urea or thiourea (3 mmol), glacial acetic acid (5 ml), and SBSSA (0.05 g) was heated with stirring at 110 °C for 1 h. After completion of the reaction (monitored by thin-layer chromatography), the catalyst was removed by filtration, and the filtrate was poured into ice water (20 ml). The resulting solid precipitate was filtered and recrystallized from ethanol to give pure 3,4-dihydropyrimidin-2(1*H*)-one or -thione. Products were identified by comparison of their ^1H and ^{13}C NMR spectra and melting points with those of authentic samples. Spectroscopic data for selected products are listed as follows.

Methyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (**4a**). m.p. 228–230 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 9.16 (br s, 1 H, NH), 7.78 (br s, 1 H, NH), 7.22–7.36 (m, 5H), 5.25 (d, 1H, $J = 2.4$ Hz), 2.24 (s, 3H), 2.07 (s, 3H); ^{13}C NMR: δ 194.4, 158.5, 152.1, 147.8, 136.9, 127.7, 113.9, 109.6, 55.1, 53.3, 30.18, 18.8.

Methyl 1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate (**4b**). m.p. 165–167 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 9.16 (br s, 1 H, NH), 7.78 (br s, 1 H, NH), 7.16 (d, 2H, $J = 8.7$ Hz), 6.88 (d, 2H, $J = 8.7$ Hz), 5.20 (d, 1H, $J = 3.0$ Hz), 3.72 (s, 3H), 2.28 (s, 3H), 2.07 (s, 3H); ^{13}C NMR: δ 194.4, 158.5, 152.1, 147.8, 136.4, 127.7, 113.9, 109.6, 55.1, 53.3, 30.2, 18.8.

Methyl 1,2,3,4-tetrahydro-6-methyl-4-(4-nitrophenyl)-2-oxopyrimidine-5-carboxylate (**4c**). m.p. 226–228 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 9.40 (br s, 1 H, NH), 8.21 (d, 2H, $J = 8.4$ Hz), 7.93 (s, 1H), 7.51 (d, 2H, $J = 8.7$ Hz), 5.39 (s, 1H), 2.32 (s, 3H), 2.19 (s, 3H); ^{13}C NMR: δ 194.0, 152.0, 151.6, 149.1, 146.7, 127.7, 123.8, 109.5, 53.1, 30.7, 19.1.

Ethyl 1,2,3,4-tetrahydro-4-isopropyl-6-methyl-2-oxopyrimidine-5-carboxylate (**4j**). m.p. 192–194 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 8.86 (br s, 1H, NH), 7.26 (br s, 1 H, NH), 4.04 (m, 2H), 3.96 (t, 1H, $J = 3.6$ Hz), 2.18 (s, 3H), 1.68 (m, 1H), 1.19 (t, 3H, $J = 7.1$ Hz), 0.82 (d, 3H, $J = 6.9$ Hz), 0.74 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR: δ 165.8, 153.2, 148.4, 98.2, 59.1, 55.5, 34.6, 18.5, 17.7, 16.0, 14.2.

2 Results and discussion

To optimize the reaction conditions, we used benzaldehyde, ethyl acetoacetate, and urea as substrates under various reaction conditions both in the absence and in the presence of SBSSA (Table 1). In the absence of catalyst, the reaction failed to give the desired product at room tempera-

Table 1 Effects of SBSSA amount, reaction temperature, and solvent on product yield

Entry	SBSSA amount (g)	Temperature (°C)	Solvent	Time (h)	Yield (%)
1	0	r.t.	HOAc	24	0
2	0	110	HOAc	10	60
3	0.05	110	HOAc	1	81
4	0.10	110	HOAc	3	81
5	0.01	110	HOAc	2	65
6	0.05	100	—	2	70
7	0.05	reflux	EtOH	5	60
8	0.05	reflux	CH_2Cl_2	10	15
9	0.05	reflux	H_2O	12	20
10	0.05	reflux	CH_3CN	6	60

Reaction conditions: benzaldehyde 2 mmol, ethyl acetoacetate 2 mmol, urea 3 mmol, solvent 5 ml.

ture, even after prolonged reaction time (24 h, entry 1). Increasing the temperature to 110 °C resulted in only a 10% yield of the desired product (entry 2) in the absence of catalyst. However, when 0.05 g of catalyst was added, the yield increased to 81% after a reaction time of only 1 h (entry 3). Increasing the amount of catalyst and the reaction time did not improve the yield further (entry 4), and decreasing the amount of catalyst and the reaction time reduced the yield (entry 5). The reaction was also carried out in various other solvents (H_2O , CH_3CN , CH_2Cl_2 , and EtOH) and under solvent-free conditions. Under these conditions, the reactions were sluggish, and the formation of byproducts was observed (entries 6–10).

To evaluate the substrate scope of the reaction, we evaluated a variety of substituted aromatic aldehydes and alkyl acetoacetate esters under the optimal reaction conditions, and we obtained good to excellent yields of the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones (Table 2). Both electron-withdrawing and electron-donating substituents on the aromatic ring of the aldehydes gave high yields of the desired products (entries 1–9, 12–14). Interestingly, an acid-sensitive carbon–carbon double was not affected by the reaction conditions, and a high yield of the desired product was obtained (entry 11). However, an aliphatic aldehyde gave a relatively low yield (entry 10). The reaction also proceeded smoothly with thiourea and various substituted aldehydes to afford 3,4-dihydropyrimidin-2(1*H*)-thiones (entries 15–18).

To further explore the substrate scope of the reaction, we replaced ethyl acetoacetate with 1,3-cyclohexanedione or dimedone. As expected, these cyclic substrates also underwent smooth, one-pot conversion to give the corresponding dihydropyrimidinones in good yields (Scheme 2). In all cases, the pure product was isolated by simple filtration, without the need for chromatography or a cumbersome workup.

Table 2 SBSSA-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones

Entry	R ¹	R ²	X	Product	Yield* (%)	Melting point (°C)	
						Found	Reported
1	C ₆ H ₅	CH ₃	O	4a	78	228–230	223–236 [31]
2	4-MeO-C ₆ H ₄	CH ₃	O	4b	80	165–167	168–170 [31]
3	4-O ₂ N-C ₆ H ₄	CH ₃	O	4c	91	226–228	228–230 [31]
4	C ₆ H ₅	OC ₂ H ₅	O	4d	81	200–202	201–203 [32]
5	4-O ₂ N-C ₆ H ₄	OC ₂ H ₅	O	4e	93	205–207	207–210 [31]
6	4-MeO-C ₆ H ₄	OC ₂ H ₅	O	4f	89	196–198	199–201 [31]
7	4-Cl-C ₆ H ₄	OC ₂ H ₅	O	4g	88	210–212	210–212 [31]
8	3-Cl-C ₆ H ₄	OC ₂ H ₅	O	4h	92	190–192	193–195 [32]
9	4-Me-C ₆ H ₄	OC ₂ H ₅	O	4i	89	212–214	215–216 [31]
10	(CH ₃) ₂ CH	OC ₂ H ₅	O	4j	43	192–194	194–195 [31]
11	PhCH=CH ₂	OC ₂ H ₅	O	4k	86	223–226	222–224 [32]
12	4-HO-C ₆ H ₄	OC ₂ H ₅	O	4l	74	203–205	202–204 [31]
13	3-Br-C ₆ H ₄	OC ₂ H ₅	O	4m	85	188–190	187–189 [32]
14	2-O ₂ N-C ₆ H ₄	OC ₂ H ₅	O	4n	71	279–281	187–189 [32]
15	C ₆ H ₅	OC ₂ H ₅	S	4o	86	205–207	208–210 [33]
16	4-MeO-C ₆ H ₄	OC ₂ H ₅	S	4p	74	146–148	150–152 [33]
17	4-Me-C ₆ H ₄	OC ₂ H ₅	S	4q	85	190–192	192–194 [33]
18	4-Cl-C ₆ H ₄	OC ₂ H ₅	S	4r	71	193–195	192–194 [33]

Reaction conditions: aldehyde 2 mmol, β-dicarbonyl compound 2 mmol, urea or thiourea 3 mmol, glacial acetic acid 5 ml, SBSSA 0.05 g, 110 °C, 1 h. *Isolated yield.

Scheme 2. SBSSA-catalyzed condensations of aldehydes, cyclic 1,3-dicarbonyl compounds, and urea.

To explore the advantages and drawbacks of this SBSSA-catalyzed reaction, we compared the results we obtained under the optimized conditions with results reported in the literature for Biginelli reactions mediated by other catalysts (Table 3). The yield of the SBSSA-catalyzed reaction was comparable to or higher than the yields obtained with all but one of the other catalysts listed in Table 3. However, all the other catalysts required longer reaction times. According to the mechanism suggested by Yamamoto [50], we have a Brønsted acid-assisted Brønsted acid catalyst catalytic system (HOAc + SBSSA), and this catalyst system showed higher activity than the other catalysts listed in Table 3.

We also evaluated the feasibility of reusing the SBSSA catalyst. We allowed benzaldehyde, ethyl acetoacetate, and urea to react under the optimized reaction conditions and

Table 3 Comparison of the SBSSA-catalyzed reaction with Biginelli reactions mediated by other catalysts

Catalyst	Temperature (°C)	Time (h)	Yield (%)	Ref.
HZSM-5	100	12	21	[46]
HY	100	12	80	[46]
Montmorillonite KSF	100	10	35	[47]
HCl*	78	18	75	—
Natural HEU type zeolite	100	4–5	75	[48]
SiO ₂ -R-SO ₃ H	80	8	90	[49]
SBSSA	110	1	81	this work

*Classical Biginelli conditions.

then filtered the reaction mixture, washed the collected solid catalyst with hot EtOH, dried it in air, and reused it in a second reaction with the same substrates. We were able to reuse the SBSSA catalyst six times without any appreciable loss in its catalytic activity (Fig. 1).

Fig. 1. Recyclability of SBSSA for one-pot synthesis of dihydropyrimidinones.

3 Conclusions

We developed a simple, new procedure for the one-pot synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones and -thiones by means of a three-component condensation catalyzed by SBSSA in acetic acid at 110 °C. This method offers several advantages: the catalyst is recyclable and inexpensive, the procedure is environmentally friendly, the reaction time is short, the yields are high, and the workup and isolation are easy.

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